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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/077,435 | 02/15/2002 | M. Vijay Kumar | M0351-268908 | 3474 |

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| EXAMINER | |
|---|---|
| DAVIS, MINH TAM B | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1642 | |

DATE MAILED: 09/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/077,435 | KUMAR, M. VIJAY | |
| | Examiner | Art Unit | |
| | MINH-TAM DAVIS | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *2-12,16-22,25,26,28-38,42,43 and 45-52* is/are pending in the application.

4a) Of the above claim(s) *2-12,16-22,25 and 26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-38,42-43,45-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.



8.0.0

## DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08/05/05 has been entered.

Applicant cancels claims 39-41, 44.

Accordingly, claims 28-38, 42-43, 45-52 are examined in the instant application.

The following are the remaining rejections.

## REJECTION UNDER 35 USC 103

Claims 28-38, 42-43, 45-52 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Bonavida, B et al, 1999, Intl J Oncology, 15(4): 793-802, of record, or Yu et al, 2000, Cancer Res, 60: 2384-2389, IDS # 128, submitted on 11/12/02, or Gliniak B et al, 1999, Cancer Res, 59 (24): 6153-6158, in view of Fathy El Etreby et al, 2000, The Prostate 42: 99-106, IDS # 27, submitted on 11/12/02 or Koide SS et al, J Reproductive Medicine, 1998, 43(7): 551-560, IDS # 53, submitted on 11/12/02, for reasons already of record in paper 04/06/05.

**A.** Applicant argues that Bonavida, Gliniak or Kiode does not teach or suggest compositions for the treatment of prostate cancer. Applicant argues that Bonavida teach using TRAIL to induce apoptosis in human mammary adenocarcima cells. Applicant argues that Gliniak teaches apoptosis induced by TRAIL in several transformed cells in vitro, but does not describe the use of TRAIL in prostate cancer. Applicant argues that Kiode et al describe the use of Mifepristone to treat cancers other than prostate cancer.

Applicant further argues that a treatment may work for one type of cancer is often ineffective to other types of cancers, and that some cells may be refractory by treatment by a particular agent.

Applicant's arguments of 08/05/05 have been considered but are found not to be persuasive for the following reasons:

It is noted that Applicant argues individual references.

Further, Contrary to Applicant's arguments, Bonavida, B et al teach that TRAIL could be used to effectively treat sensitive prostate cell lines such as CEM, at 500 ng/ml. Bonavida, B et al further teach that although there is less than 5% of cytotoxicity in prostate cancer cells DU145, PC3 and LNCaP that become resistant to TRAIL, when treated at high concentration of TRAIL at 500 ng/ml (p. 798-799), however, a combination therapy of TRAIL with chemotherapeutic drugs could reverse the resistance to TRAIL (p.797, first column).

Similarly, Yu et al teach that TRAIL induces cell death in androgen-independent prostate cancer cells PC-3 and DU145.Yu et al teach that induction of apoptosis by TRAIL is mediated by a cell death receptor, DR4, and the downstream caspases.

Further, Gliniak et al teach that TRAIL can induce apoptosis in a wide variety of transformed human cells in vitro, and that colon carcinoma displays sensitivity to TRAIL in vivo that parallel their susceptibility to TRAIL-induced apoptosis in vitro.

Thus in view of the teaching of Gliniak et al that sensitivity to TRAIL in vivo parallels their susceptibility to TRAIL-induced apoptosis in vitro, and in view that TRAIL induces cell death in prostate cancer cell lines such as androgen-independent prostate cancer cell lines, as taught by Bonavida et al, and Yu et al, one would have expected that prostate cancer would be sensitive to cell death induced by TRAIL.

Further, although Kiode et al describe the use of Mifepristone to treat cancers other than prostate cancer, Fathy El Etreby et al teach antitumor activity of Mifepristone in both androgen-sensitive (LNCaP) and androgen-insensitive ( LNCaP-C4-2) human prostate cancer cells, grown in nude mice (see Results on pages 102-103).

The motivation for combining Mifepristone and TRAIL is for treating prostate cancer, including prostate cancer cells that are resistant to TRAIL, because of the following reasons:

1) Mifepristone can kill both androgen-sensitive and –insenstive prostate cancer cells, as taught by Fathy El Etreby et al, whereas the art only discloses that TRAIL induces cell death in androgen-independent prostate cancer cells, and thus Mifepristone would be complementary to TRAIL, and

3) Although Mifepristone also kill cancer cells by apoptosis, Mifepristone function by a different mechanism than TRAIL, i.e. Mifepristone is an antiprogestin, i.e. a progesterone receptor antagonist, inhibiting progrestone-dependent processes, wherein the antitumor action by Mifepristone is mediated via the prosgesterone receptor, as taught by Fathy El Etreby et al. In other words, Mifepristone would be complementary to TRAIL, and would kill prostate cancer cells that are not killed by TRAIL, such as those resistant to TRAIL.

**B.** Applicant argues that the claimed invention is surprising results. Applicant argues that Applicant was the first to discover that Mifepristone can increase the efficacy of TRAIL in inducing apoptosis in those cancer cells that are resistant to the apoptotic effects of TRAIL.

Applicant further argues that there is nothing in the cited references that teaches or suggests the surprising synergy exhibited by the combination of TRAIL and Mifespristone, or that the combination of TRAIL and Mifepristone would be effective to treat prostate cancer cells that are refractory to TRAIL alone.

Applicant's arguments of 08/05/05 have been considered but are found not to be persuasive for the following reasons:

It is noted that the claims are drawn to a composition and not a method.

Claims 28-38, 42-43, 45-52 recite the claimed composition for use in treating prostate cancer, wherein the combination of TRAIL and the antiprogestin induces apoptosis in a greater number of the treated androgen responsive and androgen independent prostate cancer cells than the additive effect of TRAIL and the

antiprosgesterin separately applied to the cancer cells. However, this limitation is viewed as a recitation of intended use and therefore is not given patentable weight in comparing the claims with the prior art. Claims read on the ingredient per se, which is a composition comprising TRAIL and an antiprogestin, which could be Mifepristone.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

September 01, 2005